## REMARKS

Claims 1-5, 7-12, 14, 40-51, 53-58, 60, and 86-92 are currently pending. The claims stand rejected under 35 U.S.C. 112, first paragraph, 35 U.S.C. 112, second paragraph, and 35 U.S.C. 103(a).

### I. 35 U.S.C. 112, First Paragraph Rejection

Reconsideration is requested of the rejection of claims 1-5, 7-12, 14, 40-51, 53-58, 60, and 86-92 under 35 U.S.C. 112, first paragraph. The claims have been amended to cancel the phrase "preventing or reducing the risk of developing." In view of this amendment, the rejection is moot and may properly be withdrawn.

### II. 35 U.S.C. 112, Second Paragraph Rejection

Reconsideration is requested of the rejection of claims 93-97, 99-104, and 106 under 35 U.S.C. 112, second paragraph. These claims have been canceled. Therefore, the rejection is moot and may properly be withdrawn.

### III. 35 U.S.C. 101 Rejection

Reconsideration is requested of the rejection of claims 93-97, 99-104, and 106 under 35 U.S.C. 101. These claims have been canceled. Therefore, the rejection is moot and may properly be withdrawn.

### IV. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1-5, 7-12, 14, 40-51, 53-58, 60, and 86-92 under 35 U.S.C. §103(a) in view of WO 98/25896 and WO 98/40104.

Claim 1 is directed toward a method for treating a neoplasia disorder in a mammal. The method comprises administering to the mammal a therapeutically-effective amount of a selective cyclooxygenase-2 inhibitor and a DNA topoisomerase I inhibiting agent. Pursuant to an election of species requirement, applicants elected celecoxib as the selective cyclooxygenase-2 inhibitor and irinotecan as the DNA topoisomerase I inhibiting agent.

WO 98/25896 generally discloses a class of substituted pyrrolyl cyclooxygenase-2 selective inhibitors that are described as useful for treating "inflammation and inflammation-related disorders." The compounds are also said to be useful for "the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix, and skin."[1] According to WO 98/25896, the disclosed compounds may be employed in combination therapies with "steroids, NSAIDS, 5-lipoxygenase inhibitors, $LTB_4$ receptor antagonists and $LTA_4$ hydrolase inhibitors,"[2] or with "opioids and other analgesics."[3] Nowhere, however, does WO 98/25896 disclose or suggest a combination of a cyclooxygenase-2 selective inhibitor and a DNA topoisomerase I inhibiting agent for use in treating neoplasia, as required by claim 1.

WO 98/40104 discloses a class of covalent conjugates of topoisomerase I and topoisomerase II inhibitors. According to WO 98/40104, the compounds are "useful for inhibiting topoisomerase I and topoisomerase II enzymes, for promoting cellular differentiation, and for treating cancer."[4] But nowhere does the cited art disclose or suggest using the covalent conjugates in combination therapies. Moreover, nowhere does WO 98/40104 disclose or suggest a combination of a cyclooxygenase-2 selective inhibitor and a DNA topoisomerase I inhibiting agent for use in treating neoplasia, as required by claim 1.

In the absence of any disclosure of the combination employed in claim 1, a *prima facie* case for obviousness is lacking.

The Office asserts that it would have been obvious to combine two compositions (i.e., a cyclooxygenase-2 selective inhibitor and a DNA topoisomerase I inhibiting agent), each of which is disclosed in the prior art to be useful for same purpose, in order to form a third composition that is used for the very same purpose (i.e., treatment of neoplasia).[5] But the cited art, taken singly or together, provide no basis for this conclusion.

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[1]WO 98/25896 at page 6, lines 18-21.

[2]*Id.* at page 7, lines 21-26.

[3]*Id.* at page 8, lines 26-28.

[4]WO 98/40104, abstract.

[5]Paper 12152003 at page 6.

Among the many compounds and classes of compounds WO 98/25896 and WO 98/40104 propose, none offer any guidance that would have motivated a skilled artisan to prepare the combination employed in claim 1. WO 98/25896 reports that the disclosed substituted pyrrolyl cyclooxygenase-2 selective inhibitors are useful for "the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix, and skin."[6] But this disclosure is so vague and general as to be non-informative. And while WO 98/25896 considers combination therapy with the disclosed compounds and "steroids, NSAIDS, 5-lipoxygenase inhibitors, $LTB_4$ receptor antagonists and $LTA_4$ hydrolase inhibitors,"[7] or with "opioids and other analgesics,"[8] nowhere does the reference disclose or suggest a combination of a cyclooxygenase-2 selective inhibitor and a DNA topoisomerase I inhibiting agent, as required by claim 1. WO 98/40104 disclose covalent conjugates that are capable of inhibiting both topoisomerase I and II, but fail to disclose or suggest use of the conjugates in combination therapy with any other compounds, including the combination required by claim 1. Taken together, a skilled artisan empowered with the collective art of record, therefore, would not arrive at the combination of claim 1 without the benefit afforded by the applicants' patent application. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

In support of its position, the Office cites *In re Kerkhoven*.[9] *Kerkhoven*, however, is distinguishable. In *Kerkhoven*, the issue was whether the claimed process for the production of particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials was patentable. The CCPA held that it was not and, in so deciding, stated "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, **in order to form a**

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[6]WO 98/25896 at page 6, lines 18-21.

[7]*Id.* at page 7, lines 21-26.

[8]*Id.* at page 8, lines 26-28.

[9]626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

**third composition** which is to be used for the very same purpose."[10] In contrast, claim 1 is directed to a method for treating a neoplasia disorder in a mammal and not merely a method of making a third composition. Furthermore, cyclooxygenase-2 selective inhibitors interact with one or more metabolic pathways in a manner that is separate and distinct from that of a topoisomerase I inhibitor; thus, unlike in *Kerkhoven* it cannot be concluded that the use, in combination, has *the* ***very same purpose*** since the combination is being used for the purpose of interacting in metabolic pathway(s) in a manner that is distinguishable from the cyclooxygenase-2 selective inhibitor, alone, or the topoisomerase I inhibitor alone. Notably absent from the art cited by the Office is any information from which it may be concluded that such multiple interactions would be beneficial; thus, unlike the situation in *Kerkhoven*, a person of ordinary skill would not have been motivated by the art cited by the Office to use the pharmaceutical agents required by claim 1, in combination.

In *Vaeck*, the Federal Circuit held that "both the suggestion and the reasonable expectation of success must be founded in the prior art, not the applicant's disclosure."[11] Without a reasonable expectation that the combination of the two separate compounds recited in claim 1 (i.e., the cyclooxygenase-2 selective inhibitor and topoisomerase I inhibitor) would produce a composition that showed the physiological effect of treating neoplasia, the second prong of the test laid out in *Vaeck* has not been met.

According to the Office, claim 1 is obvious in view of the cited art unless the applicants can show evidence "that the combination produces unexpected results"[12] Trifan et al.[13] in fact, disclose such evidence. Trifan et al. test the combination of celecoxib (i.e., cyclooxygenase-2 selective inhibitor) and irinotecan (i.e., topoisomerase I inhibitor) in two mouse tumor models (i.e., HT-29 and colon 26 cells). According to the authors, results from the tumor models "indicate that celecoxib ***enhances*** the antitumor effect of CPT-11 [i.e., irinotecan] and reduces the severity of late diarrhea in a dose

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[10]626 F.2d at 850, 205 USPQ at 1072 (CCPA 1980), emphasis added.

[11]In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991).

[12]Paper 12152003 at page 6.

[13]Trifan et al., (2002) Cancer Research 62:5778-5784; a copy of which is enclosed with this response.

dependent manner."[14] Evidence of superior results not disclosed in the prior art is sufficient to establish non-obviousness.[15] In view of the superior results demonstrated by the applicants for the claimed combination, claim 1 is patentable over the cited art.

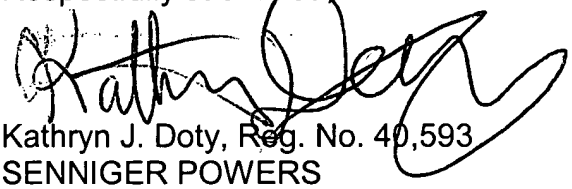
For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of the cited art. Claims 2-5, 7-12, 14, 40-51, 53-58, 60, and 86-92, recite all of the claim 1 elements, and are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements they introduce.

## V. Conclusion

In light of the foregoing, Applicants request withdrawal of the claim rejections, and solicit an allowance of the claims. The examiner is invited to contact the undersigned attorney should any issues remain unresolved.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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[14] Id. at abstract (emphasis added).

[15] *See* In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437 (Fed. Cir. 1987) and cases cited therein.